

Liquid-phase oxidation of 2-methoxy-*p*-cresol to vanillin with oxygen catalyzed by a combination of CoCl₂ and *N*-hydroxyphthalimide

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Abstract Liquid-phase oxidation of 2-methoxy-*p*-cresol to vanillin (4-hydroxy-3-methoxybenzaldehyde), in methanol, with molecular oxygen at atmospheric pressure as oxidant and a combination of cobaltous chloride and *N*-hydroxyphthalimide (NHPI) as catalyst, has been investigated. The effect of reaction conditions on conversion and selectivity for vanillin was studied systematically. Selectivity for vanillin could be enhanced by optimizing the molar ratio of 2-methoxy-*p*-cresol to NHPI, the amount of sodium hydroxide, reaction time, reaction temperature, and the volume of methanol, which determined the concentration of the reactants. Under the optimized conditions the yield of vanillin was 90.1 %.

Keywords 2-Methoxy-*p*-cresol · Vanillin · Oxidation · Molecular oxygen · Cobaltous chloride · *N*-hydroxyphthalimide

Abbreviations

NHPI *N*-hydroxyphthalimide

Introduction

Vanillin (4-hydroxy-3-methoxybenzaldehyde) is an important material extensively used in foods, cosmetics, tobacco, pharmaceuticals, and many others [1, 2]. Although vanillin as a natural product can be obtained by cultivation of vanilla plants, most of that used commercially is produced by chemical synthesis, because of its low price. Vanillin is synthesized worldwide from many starting materials including *o*-methoxyphenol [3–5], lignin [6–9], eugenol or isoeugenol [10, 11], *p*-cresol [12], and 4-hydroxybenzaldehyde [13]. From an industrial perspective the

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methods above suffer from one or several disadvantages including long reaction routes and complex production processes, scarce raw materials, low yield, expensive reagents, and serious pollution; these processes are, therefore, inefficient and cause serious effluent problems.

2-Methoxy-*p*-cresol, a natural product which can be extracted from creosote, is inexpensive and readily available. Therefore, use of 2-methoxy-*p*-cresol as a starting material to produce vanillin by one-step oxidation not only satisfies increasing demand for natural flavors but also has the advantages of low effluent disposal, good overall process economics, and high-quality product. Both environmentally and economically, use of molecular oxygen as oxidant is the best choice, because of its ready availability and water as the only by-product of the reaction. Oxidation of 2-methoxy-*p*-cresol to vanillin with molecular oxygen as oxidant has been studied [12, 14]. The process reported by Nishizawa et al. [14] was the first method of oxidation of 2-methoxy-*p*-cresol to vanillin with molecular oxygen as oxidant and soluble cobaltous chloride as catalyst; the yield of vanillin was 60 %. More recently, Chandalia and colleagues [12] used cobaltous chloride as catalyst to synthesize vanillin with air as an oxidant, but the yield of vanillin was lower than 60 %. Thereafter, several attempts were made to increase the yield of vanillin by improving the catalyst. The methodology is usually to introduce a second transition metal, for example Mn, Ni, Cu, or Fe, as cocatalyst with cobaltous chloride or oxide, to increase the selectivity for vanillin [15–19]. Some Schiff-base transition metal complexes have also been used as catalysts for oxidation of 2-methoxy-*p*-cresol to vanillin [20]. Although some improvement of the yield of vanillin has been achieved, high pressure or high temperature was needed, which resulted in the formation of hyperoxidation by-products in the reaction.

Ishii et al. [21] have successfully developed a strategy for generation of carbon radicals from hydrocarbons by use of *N*-hydroxyphthalimide (NHPI) as catalyst and oxygen as oxidant, in the presence or absence of a cobalt species, under mild conditions. This method can successfully convert alkanes into alcohols, ketones, and carboxylic acids. For example, oxidation of toluene by molecular oxygen at normal pressure and room temperature in acetic acid is achieved by the use of NHPI and Co(II) species as combined catalyst. However, achieving high selectivity for aldehydes is difficult, because of their reactivity [22, 23]. Recently, direct oxidation of aromatic alcohols and methyl aromatic compounds to aldehydes with molecular oxygen catalyzed by NHPI in the presence or absence of transition metals has been reported [24, 25]. The work indicated it was necessary to conduct the reaction in neutral or alkaline medium to achieve high selectivity for aldehydes. This suggests the combination of NHPI and cobaltous chloride as catalyst may enable efficient oxidation of 2-methoxy-*p*-cresol to vanillin in alkaline medium. Preliminary experiments confirmed the hypothesis was plausible. Therefore, the effects of different reaction conditions, for example reaction time, temperature, catalyst loading, solvent volume, and quantity of base on the conversion of 2-methoxy-*p*-cresol and selectivity for vanillin were investigated. Herein, we report the results of the investigation.

Materials and methods

Materials and apparatus

NHPI was purchased from Acros Organics. 2-Methoxy-*p*-cresol, cobaltous chloride ($\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$), sodium hydroxide (NaOH), and HPLC-grade methanol, acetonitrile, and phosphoric acid were obtained from Tianjin Fuchen Chemical Reagent Factory, China. All the chemicals were used as received. HPLC was performed with a Shimadzu (Kyoto Japan) SPD-10ATvp plus chromatograph equipped with an SPD-10Avp detector and C₁₈ reversed-phase column (4.6 mm i.d. \times 250 mm). The mobile phase was 25 % acetonitrile–water containing 0.1 % phosphoric acid.

Catalytic procedure

Oxidation reactions were conducted in a 10-ml two-necked flask equipped with a condenser and a thermometer. A balloon filled with oxygen was connected to the top of the condenser. All reactions were conducted at atmospheric pressure and stirred with an electromagnetic stirrer at a constant rate.

In a typical process, a mixture of NaOH (21.7 mmol) and methanol (3.0 ml) was introduced into the flask. The mixture was vigorously stirred at room temperature. When the NaOH had dissolved completely, 2-methoxy-*p*-cresol (3.6 mmol) was introduced and the mixture was stirred for half an hour to ensure the substrate had been converted into its sodium salt. Cobaltous chloride and NHPI were then added quickly. Chilled water was circulated through the condenser to minimize loss of the solvent. The mixture was heated to the desired temperature (65 °C), then the oxygen from the balloon was introduced, and controlled by use of a triple valve. After a specific time, introduction of oxygen was stopped and the reaction mixture was left to cool to room temperature. The cooled reaction mixture was analyzed as described below.

Analysis of the reaction mixture

After reaction the whole reaction mixture was accurately weighed to obtain the total weight (w_t). An accurately weighed amount (approx. 0.1 g) of the reaction mixture (w_0) was placed in a 10-ml volumetric flask, then an appropriate amount of concentrated hydrochloric acid was added to neutralize the NaOH and the sodium salt of the substrate and product. The neutralized mixture was dissolved in mobile phase to a constant volume. The amounts of 2-methoxy-*p*-cresol and vanillin (w_{s0} and w_{v0}) were determined by HPLC with use of an external standard.

The weight of vanillin in the reaction mixture can be obtained by use of Eq. 1:

$$w_v = (w_t \times w_{v0}) / w_0(\text{g}) \quad (1)$$

The weight of 2-methoxy-*p*-cresol left in the reaction mixture can be obtained by use of Eq. 2:

$$w_s = (w_t \times w_{s0}) / w_0(g) \quad (2)$$

$$\text{Conversion}(\%) = \frac{\text{moles of 2-methoxy-}p\text{-cresol reduced}}{\text{moles of 2-methoxy-}p\text{-cresol charged}} \times 100 \% \quad (3)$$

$$\text{Selectivity}(\%) = \frac{\text{moles of vanillin obtained}}{\text{moles of 2-methoxy-}p\text{-cresol reduced}} \times 100 \% \quad (4)$$

$$\text{Yield} = \text{Conversion} \times \text{Selectivity} \quad (5)$$

Results and discussion

A few preliminary experiments showed the reaction proceeded readily when catalyzed by a combination of cobaltous chloride and NHPI in the presence of NaOH in methanol under atmospheric oxygen pressure at elevated temperature. The selectivity for vanillin was lower than 70 %, because of the formation of side products, for example 3-methoxy-4-hydroxybenzyl alcohol, 3-methoxy-4-hydroxybenzyl methyl ether, 3-methoxy-4-hydroxybenzoic acid, and tarry material. To obtain vanillin with high selectivity the effects of reaction time, amounts of NHPI and NaOH, reaction temperature, and solvent volume were studied.

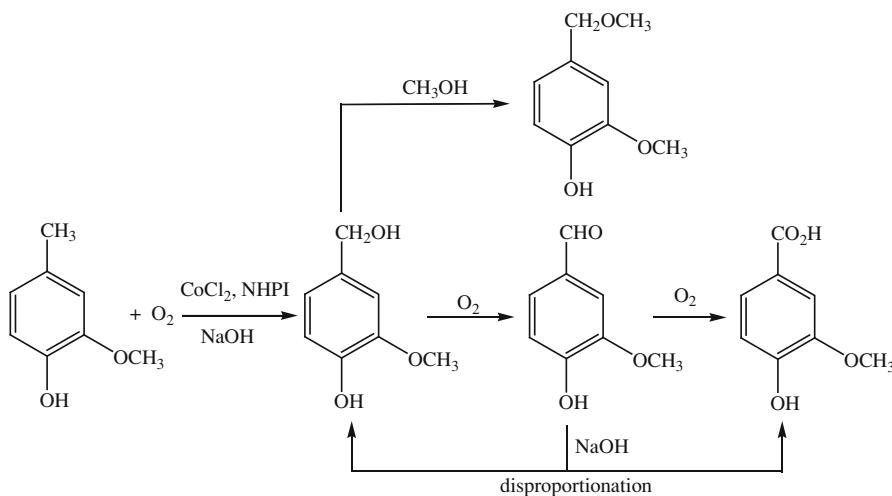
Effect of reaction time

First, the effect of reaction time on the reaction was investigated at 50 °C; the results are shown in Table 1. It can be seen that conversion of 2-methoxy-*p*-cresol increased with time, as expected, and was >99.0 % after 6 h. Selectivity for vanillin also increased with time, initially, reaching a maximum after reaction for 7 h, after which it decreased gradually with time. GC–MS analysis indicated the main product was vanillin, with 3-methoxy-4-hydroxybenzyl alcohol as major by-product and other, minor, by-products including 3-methoxy-4-hydroxybenzoic acid and 3-methoxy-4-hydroxybenzyl methyl ether (Fig. 1). In fact, much work has focused on oxidation of *p*-cresol to *p*-hydroxybenzaldehydes with oxygen similar to that of

Table 1 Effect of reaction time on the oxidation of 2-methoxy-*p*-cresol

Entry	Time (h)	Conversion (%)	Selectivity (%)	Yield (%)
1	2	60.0	50.0	30.0
2	4	85.0	58.0	49.3
3	6	>99.0	66.7	66.7
4	7	>99.0	72.2	72.2
5	8	>99.0	68.6	68.6
6	9	>99.0	64.9	64.9

Reaction conditions: 2-methoxy-*p*-cresol 3.623 mmol, molar ratio of sodium hydroxide to 2-methoxy-*p*-cresol 5.7:1, cobaltous chloride 0.017 mmol, NHPI 0.072 mmol, reaction temperature 50 °C, methanol 5 ml, atmospheric oxygen pressure

**Fig. 1** Pathways of formation of vanillin and by-products

2-methoxy-*p*-cresol to vanillin [26–28]. On the basis of the results obtained by GC–MS analysis and reported in literature we can infer the formation pathways of vanillin and by-products (Fig. 1).

From the pathways it is obvious that 2-methoxy-*p*-cresol was first oxidized to 3-methoxy-4-hydroxybenzyl alcohol, a key intermediate in the reaction. This intermediate was then transformed to vanillin with time, which increased the selectivity for vanillin. With the reaction time was extended further, some vanillin was converted into to 3-methoxy-4-hydroxybenzoic acid by over oxidation or disproportionation (Fig. 1). As a result, selectivity for vanillin decreased.

Effect of NHPI loading

The effect of amount of NHPI on the oxidation reaction was studied at 50 °C keeping the amount of cobaltous chloride constant at 0.017 mmol. The results are given in Table 2, from which it can be seen that conversion of 2-methoxy-*p*-cresol was always higher than 99.0 % after 7 h; however, selectivity for vanillin changed with amount of NHPI. Selectivity for vanillin was only 59.5 % if no NHPI was used

Table 2 Effect of NHPI loading on the oxidation of 2-methoxy-*p*-cresol

Entry	NHPI/substrate (mol %)	Conversion (%)	Selectivity (%)	Yield (%)
1	0	>99.0	59.5	59.5
2	1	>99.0	65.0	65.0
3	2	>99.0	72.2	72.2
4	4	>99.0	65.1	65.1

Reaction conditions: 2-methoxy-*p*-cresol 3.623 mmol, molar ratio of sodium hydroxide to 2-methoxy-*p*-cresol 5.7:1, cobaltous chloride 0.0173 mmol, reaction temperature 50 °C, reaction time 7 h, methanol 5 ml, atmospheric oxygen pressure

and increased to 72.2 % when the amount of NHPI was increased to 2 % of the amount of 2-methoxy-*p*-cresol. The selectivity for vanillin then began to decrease with further increase in amount of NHPI. According to the literature, neat NHPI can catalyze the oxidation of benzyl alcohols by molecular oxygen, forming the corresponding aldehydes [29, 30]. As shown in Fig. 1, the reaction producing vanillin proceeded with 3-methoxy-4-hydroxybenzyl alcohol as intermediate, hence, low NHPI loading suppressed further oxidation of 3-methoxy-4-hydroxybenzyl alcohol to vanillin; high NHPI loading accelerated the transformation process, which increased selectivity for vanillin for a specific time. However, if the NHPI loading is too high, the intermediate 3-methoxy-4-hydroxybenzyl alcohol will be quickly transformed to vanillin, thus increasing the contact time of vanillin with oxygen and NaOH. As a result some of the vanillin generated is turned into 3-methoxy-4-hydroxybenzoic acid, as shown in Fig. 1.

Effect of temperature

The effect of temperature on both conversion of 2-methoxy-*p*-cresol and selectivity for vanillin was studied in the temperature range 45–70 °C. The results, listed in Table 3, indicated that conversion was higher than 99.0 % in this temperature range. Selectivity for vanillin increased from 57.5 to 80.8 % when the temperature was increased from 45 to 70 °C, remaining almost constant in the range 65–70 °C. Because the reaction was carried out at atmospheric pressure and the solvent was methanol, the effects of temperature higher than 70 °C could not be determined. One reason for the high selectivity for vanillin at high temperature is that high temperature promotes transformation of the intermediate to vanillin. Another reason is that NaOH was not completely dissolved at lower temperatures, as has also been observed by others for similar conditions [28]. Incomplete dissolution of NaOH prevented complete conversion of 2-methoxy-*p*-cresol to its sodium salt, which left some free 2-methoxy-*p*-cresol to form some other oxidation-coupling products under these reaction conditions.

Table 3 Effect of temperature on the oxidation of 2-methoxy-*p*-cresol

Entry	Temperature (°C)	Conversion (%)	Selectivity (%)	Yield (%)
1	45	>99.0	57.5	57.5
2	50	>99.0	72.2	72.2
3	55	>99.0	73.8	73.8
4	60	>99.0	78.0	78.0
5	65	>99.0	80.2	80.2
6	70	>99.0	80.8	80.8

Reaction conditions: 2-methoxy-*p*-cresol 3.623 mmol, molar ratio of sodium hydroxide to 2-methoxy-*p*-cresol 5.7:1, cobaltous chloride 0.0173 mmol, NHPI 0.0725 mmol, reaction time 7 h, methanol 5 ml, atmospheric oxygen pressure

Effect of amount of sodium hydroxide

The concentration of (NaOH) has significant effect on the liquid-phase oxidation of methyl aromatic compounds, including alcohols [26, 28]. Hence, it was important to study the effect of NaOH concentration on 2-methoxy-*p*-cresol oxidation. The experiments were conducted by varying the molar ratio of NaOH to 2-methoxy-*p*-cresol from 4.5 to 6.5 for a constant amount of 2-methoxy-*p*-cresol (3.623 mmol) in 5 ml methanol at 65 °C. The results, shown in Table 4, indicate that conversion was higher than 99.0 % and that selectivity for vanillin increased from 61.1 to 84.0 % in the NaOH-to-substrate molar ratio range from 4.5:1–6.5:1. It was observed that a large excess of sodium was necessary to maintain high selectivity for vanillin. Even when the NaOH to 2-methoxy-*p*-cresol molar ratio was 5.5, by-product formation was still more than 25.0 %. Lower selectivity for vanillin under these conditions was because of oxidative dimerization of 2-methoxy-*p*-cresol (Fig. 2), similar to dimerization of *p*-cresol in its liquid-phase oxidation [28]. It is known that the phenolic hydroxyl group of *p*-cresol derivatives interferes with oxidation of the substrates to their corresponding aldehydes [26, 28], it is necessary to completely convert *p*-cresol derivatives into their sodium phenolate salts with a large excess of NaOH; this reduces oxidative dimerization of 2-methoxy-*p*-cresol.

Effect of volume of methanol

The volume of methanol affects the concentrations of the reactants in the mixture. It is, therefore, a crucial condition that must be studied. The effect of volume of methanol on the reaction was studied in the range 2–6 ml while keeping the amounts of the other reactants constant. The results, listed in Table 5, indicate that conversion of 2-methoxy-*p*-cresol was always higher than 99.0 %. However, selectivity for vanillin was found to change with methanol volume. Selectivity for vanillin increased sharply from 77.6 % to a maximum of 90.1 % when the volume of methanol was increased from 2 to 3 ml; it then decreased slowly as the volume of methanol was increased further, and reached 76.3 % when the volume of methanol 6 ml. It was found that low methanol volume resulted in a viscous reaction medium that affected mass transfer of the reactants. If the volume of methanol was too high,

Table 4 Effect of amount of sodium hydroxide on the oxidation of 2-methoxy-*p*-cresol

Entry	NaOH/substrate (mol:mol)	Conversion (%)	Selectivity (%)	Yield (%)
1	4.5	>99.0	61.1	61.1
2	5.0	>99.0	74.1	74.1
3	5.5	>99.0	79.7	79.7
4	5.7	>99.0	80.2	80.2
5	6.0	>99.0	83.3	83.3
6	6.5	>99.0	84.0	84.0

Reaction conditions: 2-methoxy-*p*-cresol 3.623 mmol, cobaltous chloride 0.0173 mmol, NHPI 0.0725 mmol, reaction temperature 65 °C, reaction time 7 h, methanol, 5 ml, atmospheric oxygen pressure

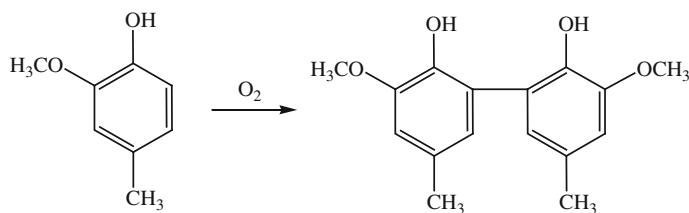


Fig. 2 Oxidative dimerization of 2-methoxy-*p*-cresol

Table 5 Effect of volume of methanol on the oxidation of 2-methoxy-*p*-cresol

Entry	Methanol (ml)	Conversion (%)	Selectivity (%)	Yield (%)
1	2	>99.0	77.6	77.6
2	3	>99.0	90.1	90.1
3	4	>99.0	84.7	84.7
4	5	>99.0	83.3	83.3
5	6	>99.0	76.3	76.3

Reaction conditions: 2-methoxy-*p*-cresol 3.623 mmol, molar ratio of sodium hydroxide to 2-methoxy-*p*-cresol 6.0:1, cobaltous chloride 0.0173 mmol, NHPI 0.0725 mmol, reaction temperature 65 °C, reaction time 7 h, atmospheric oxygen pressure

however, this resulted in low reactant (e.g. NaOH) concentration, leading to dimerization of 2-methoxy-*p*-cresol (Fig. 2) and nucleophilic attack of CH₃O⁻ on the benzyl carbon of the intermediate 3-methoxy-4-hydroxybenzyl alcohol, leading to the formation of 3-methoxy-4-hydroxybenzyl methyl ether, as observed by others [28, 31, 32].

Conclusions

Liquid-phase oxidation of 2-methoxy-*p*-cresol with atmospheric oxygen as oxidant, catalyzed by a combination of cobaltous chloride and NHPI in the presence of NaOH, has been used for synthesis of vanillin. The effect of reaction conditions on conversion and selectivity for vanillin was studied systematically. This investigation showed that selectivity for vanillin was strongly dependent on reaction time, reaction temperature, molar ratio of NHPI to substrate, amount of NaOH, and volume of methanol, which determines the concentration of the reactants. Under the optimized conditions—2-methoxy-*p*-cresol 3.623 mmol, molar ratio of NaOH to 2-methoxy-*p*-cresol 6.0:1, cobaltous chloride 0.0173 mmol, NHPI 0.0725 mmol, methanol 3 ml, reaction temperature 65 °C, and reaction time 7 h—the yield of vanillin reached 90.1 %. This process is not only economic but also environmental friendly.

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